U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
SECRETARY'S ADVISORY COMMITTEE ON XENOTRANSPLANTATION

INFORMED CONSENT IN CLINICAL RESEARCH INVOLVING XENOTRANSPLANTATION

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SACX REPORT ON INFORMED CONSENT IN CLINICAL RESEARCH INVOLVING XENOTRANSPLANTATION

Outline

EXECUTIVE SUMMARY

I. BACKGROUND

II. ETHICAL FOUNDATIONS AND FUNCTIONS OF INFORMED CONSENT

III. COMPONENTS OF INFORMED CONSENT
- A. Disclosure
- B. Comprehension
- C. Voluntariness

IV. THE INFORMED CONSENT PROCESS
- A. Points to Convey in the Informed Consent Process
- B. The Informed Consent Team
- C. Factors That Facilitate the Informed Consent Process: Setting, Format, and Pacing

V. INFORMED CONSENT FORMS

VI. ADULT INFORMED CONSENT FORM
- A. Protocol
- B. Purposes
- C. Treatment Choices
- D. Participation
  1. Who Can Enroll
  2. Who Cannot Enroll
  3. Duration of Involvement
  4. Chance Assignment (Randomization) to Treatment Groups
- E. Study Procedures
  1. Screening Visits, Assessments, and Tests
  2. Rating Scales
  3. Surgical Procedures
  4. Medications
  5. Diaries
  6. Follow-Up
- F. Risks
  1. Rejection/Failure of the Procedure
  2. Immunosuppression
  3. Animal-to-Human Infections
  4. Possible Discomforts and Quality-of-Life Issues

5. Possibility of Being Isolated or Quarantined
6. Loss of Confidentiality
7. Possibility That This Study Will Be Ended Early
8. Additional Risks

G. Responsibilities
H. Benefits
I. Costs and Compensation
J. Confidentiality
K. Voluntary Enrollment Accompanied by an Agreement to Follow Responsibilities
L. Contact Information

VII. SPECIAL ISSUES RAISED BY XENOTRANSPLANTATION

A. Public Safety Measures
1. Quarantine and Lifelong Surveillance
2. Public Health Laws

B. Issues Involving Third Parties
1. Intimate Contacts
2. Health Care Professionals
3. Community Consent

C. Children and Incapacitated Adults
1. Determining Decision-Making Incapacity
2. Federal and Other Guidance in Clinical Trials
3. Xenotransplantation for Incapacitated Adults
4. Participation of Children in Xenotransplantation Research

VIII. RECOMMENDATIONS

References

INFORMED CONSENT IN CLINICAL RESEARCH INVOLVING XENOTRANSPLANTATION

EXECUTIVE SUMMARY

This report of the Secretary's Advisory Committee on Xenotransplantation (SACX) is intended to provide Institutional Review Boards (IRBs) and clinical investigators with a thorough and systematic discussion of informed consent for clinical procedures that involve exposing humans to xenotransplantation products. In addition to discussing a number of unique issues and problems, this report addresses an overarching issue that is not unique to xenotransplantation: the challenge of securing informed consent for clinical research that involves complex procedures. In this sense, this report is also designed to be a model discussion of informed consent that applies to complex research in general.

Xenotransplantation research raises special challenges that pertain to informed consent, including the following:

- Public health risks, such as the transmission of infectious agents in pig-to-human xenotransplantation, and how these risks should be monitored and managed

- The need to inform intimate contacts, health care professionals, and the general public about issues relating to xenotransplantation

- Informing third parties, such as the intimate contacts of research participants (herein also referred to as "subjects") or the public at large about the risks associated with xenotransplantation

- The potential participation of persons who are incapable of giving consent (e.g., adults with compromised decision-making capacity, children) in xenotransplantation research

The informed consent process upholds an essential and profound set of ethical values and legal principles. Similar to earlier innovative areas of medical research, xenotransplantation calls for renewed reflection and additional guidelines concerning the nature and complexities of informed consent.

Foundations and Components of Informed Consent

The consent process upholds an essential and profound set of ethical values and legal principles. Similar to earlier innovative areas of medical research, xenotransplantation calls for renewed reflection and additional guidelines concerning the nature and complexities of informed consent. Informed consent preserves the values of self-determination, freedom of choice, and protection from harm, abuse, and deception. These values are rooted in the basic ethical principles of

beneficence (i.e., maximizing benefits in relation to potential harms) and respect for human beings as autonomous agents.

The foundations of informed consent include (1) ***disclosure*** of relevant information on the part of researchers through discussions and materials; (2) ***comprehension*** by prospective research participants; and (3) ***voluntariness*** on the part of prospective research participants.

The Informed Consent Process As It Pertains to Xenotransplantation

The task of fully disclosing information regarding xenotransplantation is especially challenging, given the complexity of xenotransplantation, the attendant public health risks, and the involvement of subjects whose physical and emotional health may already be compromised. Careful consideration of the informed consent process is necessary, including the content, setting, format, and pacing of the communication that occurs. It may also be advisable to include in these discussions certain individuals in addition to the subject, such as his or her family members and intimate contacts. Inclusion of these individuals must be voluntary and in accord with the subject's confidentiality and privacy rights.

Points to Convey in Securing Informed Consent

Discussions to facilitate obtaining an individual's informed consent to undergo xenotransplantation should include the following:

- Background and history of the particular procedure, including previous related trials and outcomes and relevant results from animal studies
- A description of the procedure(s) to be followed, including identification of those that are experimental
- A description of the risks and potential benefits, if any, of the procedure
- Available alternatives (both accepted medical practices and other experimental approaches), including their comparative risks and benefits
- Possible social, economic, psychological, and/or medical consequences to the subject and his or her family
- Measures to protect, and the potential for breaches of, the privacy and confidentiality of research subjects
- Responsibilities of the recipients of xenotransplantation products, such as the need for lifelong follow-up; collection, testing, and archiving of biological samples; behavioral modifications; the continued need to inform intimate contacts and future health care providers; and deferral of donation of blood and other body fluids and tissues

- A request for autopsy

The Informed Consent Team

Due to the medical complexity of xenotransplantation, the lifetime commitment expected of the recipient, and the potential public health, psychosocial, and financial issues associated with the procedure, the informed consent process should involve a team of individuals with the expertise to educate the potential recipient about each of these areas. The members of this "consent team" should facilitate the subject's comprehension of the information that has been provided and should use these discussions to determine whether the individual is entering into the study voluntarily, rather than in response to pressure from external sources. At a minimum, the consent team should comprise the following:

- The principal investigator, who provides basic medical and scientific information about the xenotransplantation procedure

- An individual who is knowledgeable about post-transplant care and the long-term responsibilities of xenotransplantation recipients

- An individual(s) with expertise in the social, psychological, and financial implications of xenotransplantation

The potential recipient should be informed that others may also be consulted to help address additional issues related to xenotransplantation, such as a religious advisor, a recipient of a xenotransplantation product, and a physician who is independent of the research team.

Facilitating the Informed Consent Process

A series of discussions are necessary for the members of the consent team to convey, and prospective participants to comprehend, the volume of complex information involved with xenotransplantation. These discussions should:

- Take place in a setting that affords privacy, comfort, and freedom from disruption;

- Be face-to face, not excessively lengthy, and separated in time to allow the prospective subject to assimilate the information provided at each meeting; and

- Use language, both written and oral, at the level of the prospective subject's understanding, with medical and scientific jargon kept to a minimum and translated in the language with which the prospective subject is fluent.

To provide support to prospective subjects and to facilitate their retention and comprehension of information, they should be encouraged to include their significant others or other advisors in discussions about xenotransplantation.

Informed Consent Forms

The signing of a consent form is neither the goal nor the end point of the informed consent process, but rather a single element in a larger, multifaceted strategy of disclosure, comprehension, and voluntariness. Informed consent forms should use ordinary language, explain technical terminology, and be formatted in ways that facilitate comprehension and recall. In the full version of this report, the SACX proposes a model for a clear, well-formatted, comprehensive, and understandable consent form for xenotransplantation protocols.

Special Issues Raised by Xenotransplantation

Researchers and IRB members alike need to know about special problems and concerns raised by xenotransplantation clinical research so that they can provide appropriate explanations in the consent forms and throughout the informed consent process. These special issues include public safety measures, third parties, and the participation of children and incapacitated adults in xenotransplantation procedures.

Public Safety Measures

Because xenotransplantation research presents the risk of spreading new infectious diseases, both conventional and innovative public safety monitoring measures may be needed. To ensure that public health authorities are able to detect and isolate new infectious agents, it is essential for prospective xenotransplantation research participants to be fully informed that their compliance with lifelong surveillance is critical and that failure to comply may, in some cases, necessitate the application of public health laws. For example, if it is determined that the recipient of a xenotransplantation product has an infectious disease that poses a serious and imminent health threat to others, and the recipient fails to voluntarily comply with public health protection measures, public health laws could be used for detention and quarantine. The U.S. Supreme Court has clearly endorsed the authority of a state to enact quarantine and other public health laws.

Issues Involving Third Parties

The risks of transmission of infectious disease warrant serious consideration not only by research participants but also their intimate contacts and health care workers who come in contact with the recipient. It has therefore been argued that obtaining informed consent from research participants alone is not enough and that there is an ethical obligation to involve other individuals who could be at risk. Currently, there is no legal foundation in the U.S. for obtaining informed consent from third parties, unless the study expressly includes third parties in the research. The informed consent process for xenotransplantation research should include a component that informs the recipient of his or her responsibility to educate current and future intimate contacts about the possibility of xenogeneic infections. Current federal guidance recommends that, during the consent process, the consent team offer assistance in this educational effort and address uncertainties about the risks of xenogeneic infections, behaviors known to transmit infectious agents, and methods to minimize the risk of transmission.

Recipients should also be informed of the need to educate their current and future intimate contacts about the importance of reporting significant unexplained illness to the institution where the xenotransplantation procedure was performed, to their primary care provider, or to a local public health department.

Health care workers who come in contact with xenotransplantation recipients also face the risk of xenogeneic and zoonotic infections. Accordingly, the informed consent process for xenotransplantation research should include a component that advises recipients of their responsibility to inform their current and any future health care providers about their receipt of a xenotransplantation product.

The notion of community consent for xenotransplantation research has been the subject of considerable controversy, both nationally and internationally, and poses many difficulties. In light of the difficulty inherent in the notion of "community consent," SACX suggests that it or some other appropriately constituted advisory committee should continue to serve as the mechanism for ensuring ongoing education and discourse in the lay community about public health concerns, as well as other social, medical, and ethical issues raised by xenotransplantation clinical research.

Participation of Children and Incapacitated Adults

The ability to fully and successfully address the elements of informed consent is compromised when the prospective research participant is an impaired adult or a child who is not capable of comprehending the complex information that attends their potential participation. Federal laws governing informed consent in research address situations in which some research participants may not be capable of rendering informed consent.

The process of obtaining informed consent in the context of xenotransplantation is further complicated when consent would need to be rendered by a legal surrogate or proxy decision-maker on behalf of an incapacitated research participant. Considering all of these factors, the SACX recommends that at this time, enrollment of mentally impaired individuals into xenotransplantation protocols should be limited to those in whom mental capacity is likely to be restored by the procedure. In these circumstances, the incapacitated patient may participate in xenotransplantation research if the surrogate decision-maker has evidence that the individual would have wanted to participate in the xenotransplantation protocol, or if the surrogate decision-maker determines that the individual's enrollment would promote the patient's best interests.

Informed consent for research has been the subject of considerable debate in the field of pediatrics. At this time, given that clinical xenotransplantation research is in the earliest experimental stages, and given the commitment of lifelong medical monitoring required of all xenotransplantation research participants, the SACX recommends that, as a general matter, children should not participate in xenotransplantation protocols. However, there may be exceptions to this general rule, such as special circumstances in which the potential benefit to a child from a xenotransplantation procedure is high given the available alternatives. These

situations should be considered on a case-by-case basis, and applicable regulations concerning children's participation in research must be followed.

Recommendations

1. The informed consent process used with respect to competent adults in clinical research involving xenotransplantation should ensure that (a) information disclosed is sufficiently complete, (b) the participant comprehends the information disclosed, and (c) the participant's consent to participate is voluntary.

2. The goals of the informed consent process should be facilitated by the following

   a. Involving a "consent team" comprising (at a minimum) the principal investigator, a researcher team member who is knowledgeable about post-transplant care and the long-term responsibilities of recipients, and an individual(s) who has expertise in the social, psychological, and financial implications of xenotransplantation

   b. Holding a series of face-to-face discussions with the prospective xenotransplantation recipient in a setting that affords privacy and comfort, and using comprehensible language

   c. Using an informed consent form that includes specific elements required by the Common Rule and 21 CFR 50 and 56 as well as information recommended by the U.S. Public Health Service, the Department of Health and Human Services, and the Food and Drug Administration (FDA) and that is written in a manner that will help ensure understanding

3. To protect against the potential spread of new diseases, the informed consent process should include the prospective participant's understanding and agreement to comply with public safety measures (including lifelong monitoring, temporary isolation if indicated, and autopsy) and to inform family members, current and future intimate contacts, and health care personnel about the possibility of transmission of xenogeneic infection.

4. Public health authorities should maintain good communication with physicians and other health care providers who are likely to serve as the first line of defense against a new disease that emerges in a xenotransplantation recipient.

5. Legislatures should evaluate the effectiveness of current public health laws to address situations in which an asymptomatic xenotransplantation recipient fails to comply with surveillance instructions, and they should consider appropriate amendments to those laws if needed.

6. Health care workers who will be involved in xenotransplantation procedures should be informed in advance of the known and potential risks of xenogeneic infections posed by the procedure, behaviors known to transmit infectious agents, methods to minimize that risk, the need to report significant unexplained illness, and the plans of the sponsor and/or the center

where the procedure is performed for monitoring health care workers and for post-exposure evaluation and management.

7. The sponsor or institution where the xenotransplantation procedure is performed should have plans for monitoring involved health care workers and plans for post-exposure evaluation and management and should ensure that infection control measures are adhered to.

8. The SACX (or another appropriately constituted advisory committee) should continue to serve as a mechanism for ensuring ongoing education and discourse in the lay community about public health concerns, as well as other social, medical, and ethical issues raised by xenotransplantation clinical research, through the following:

a. Providing a forum for public discussion of xenotransplantation issues, as appropriate, and ensuring that the members of the advisory body are available for interviews;

b. Being informed about xenotransplantation protocols so that it can knowledgeably communicate with the community about pertinent social, public health, medical, and ethical issues;

c. Developing and making available informational resources on xenotransplantation;

d. Making recommendations to the DHHS Secretary on policy and procedures, following consensus developed by the committee's multidisciplinary membership; and

e. Developing closer relationships with relevant groups in other nations.

9. At present, enrollment of incapacitated adults into xenotransplantation protocols should be limited to situations in which:

a. The individual's mental capacity is likely to be restored by the procedure;

b. The individual's legally authorized surrogate decision maker determines that the individual's enrollment in the protocol accords with the individual's likely preferences under the circumstances or, if these preferences are unknown, that enrollment would promote the individual's best interests;

c. The individual's legally authorized surrogate represents that the individual is a responsible person and is likely to adhere to lifelong follow-up responsibilities; and

d. There are plans for assistance with life-long follow-up requirements in the event that such assistance is needed.

10. At this time, as a general matter, children should not participate in xenotransplantation protocols. There may be special circumstances, however, in which the possibility of benefit to a

child is high, given available alternatives. Researchers and institutions should consider these situations on a case-by-case basis and should pursue further study of this issue.

INFORMED CONSENT IN CLINICAL RESEARCH INVOLVING XENOTRANSPLANTATION

The U.S. Department of Health and Human Services (DHHS) has a vital role in safeguarding public health while fostering the development of promising strategies to treat disease and disability. Xenotransplantation is one such strategy for treating certain types of tissue destruction, organ failure, and other health conditions. The complex safety, ethical, legal, and social issues raised by xenotransplantation transcend the mission and purview of any single DHHS agency. In recognition of this, the DHHS established the Secretary's Advisory Committee on Xenotransplantation (SACX) to consider the full range of scientific, medical, social, ethical, and public health concerns raised by xenotransplantation and to make recommendations to the Secretary on policies and procedures that are relevant to all aspects of the scientific development and clinical application of xenotransplantation.

> **Xenotransplantation** refers to any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source; or (b) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

The SACX is charged with the following:

- Advise DHHS on the current state of knowledge regarding xenotransplantation.
- Be informed about current and proposed xenotransplantation clinical trials in order to identify and discuss the medical, scientific, ethical, legal, and/or socioeconomic issues raised by these trials;
- Advise on the potential for transmission of infectious diseases as a consequence of xenotransplantation.
- Advise on policies relevant to xenotransplantation, including the need for changes to the *PHS Guideline on Infectious Disease Issues in Xenotransplantation*.[1]
- Discuss additional scientific, medical, public health, ethical, legal, and socioeconomic issues, including international policies and developments, that are relevant to xenotransplantation.

BACKGROUND

There are many issues associated with xenotransplantation that merit in-depth attention and discussion.[2–9,*] The SACX has chosen to focus this report on the unique and complex issues of

[*] For example, ethical and legal concerns that have been identified and discussed at length in the medical, legal, and bioethics literature[2–9] include the risks of introducing infectious disease into the general public; the "naturalness" or "unnaturalness" of transplants from non-human animals to humans; the genetic manipulation and use of nonhuman

informed consent in clinical research involving xenotransplantation. Limited clinical research involving xenotransplantation of cells and tissues is already under way, and clinical trials involving solid-organ transplants from animals to humans may occur in the foreseeable future. Current realities, as well as foreseeable expectations, endow this topic with a sense of immediacy.

This report is intended to provide Institutional Review Boards (IRBs) and clinical investigators with a thorough and systematic discussion of informed consent for clinical procedures that involve exposing humans to xenotransplantation products. In addition to discussing a number of unique issues and problems, the report addresses an overarching issue that is not unique to xenotransplantation: the challenge of securing informed consent for clinical research that involves complex procedures. In this sense, this report is designed to be a model discussion of informed consent that applies to complex research in general.

Xenotransplantation research raises special challenges that pertain to informed consent, including the following:

- Public safety risks, such as the transmission of infectious agents in pig-to-human xenotransplantation, and how these risks should be monitored and managed

- Issues relating to the need to inform intimate contacts, health care professionals, and the general public about issues relating to xenotransplantation

- Questions surrounding the need to obtain informed consent from third parties, such as the intimate contacts of research participants (herein also referred to as "subjects") or the public at large

- Xenotransplantation research involving persons who are incapable of giving consent (e.g., adults with compromised decision-making capacity, children)

ETHICAL FOUNDATIONS AND FUNCTIONS OF INFORMED CONSENT

Revolutionary changes in medical practice and research occurred when practicing physicians were required to obtain the informed consent of their patients for treatment and researchers were required to obtain informed consent from prospective participants in clinical research.[10] The consent process upholds an essential and profound set of ethical values and legal principles. Similar to earlier innovative areas of medical research, xenotransplantation calls for renewed reflection and additional guidelines concerning the nature and complexities of informed consent. The challenges of xenotransplantation research cannot be met simply by making informed consent forms longer and more complex.

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animals; what level of preclinical success would warrant clinical xenotransplantation trials with solid organs; whether it is just to consume significant resources to benefit a limited number of patients; and issues related to prospective research participants' informed consent for xenotransplantation.

The ethical foundations of informed consent emerge when we ask why the process of securing consent is required before research involving human subjects can be initiated. The short answer is that consent is mandated by federal regulation.[11,12] The longer answer is that informed consent preserves the values of self-determination, freedom of choice, and protection from harm, abuse, and deception.[13–15] These values are rooted in the basic ethical principles of beneficence (i.e., maximizing benefits in relation to potential harms) and respect for human beings as autonomous agents.[16]

The relationships between these values and informed consent are depicted in codes of medical ethics, court cases, federal regulation and state legislation, and numerous publications. The first article of the *Nuremberg Code* states, "The voluntary consent of the human subjects is absolutely essential."[17, pp.181–182] Initially composed to bring criminal charges against Nazi physicians who operated completely outside the limits of ethical practice when they conducted brutal research on nonconsenting prisoners, the *Code* stresses that the free and voluntary consent of the subject functions to protect research participants from deceit, fraud, force, and intentional harm.[18]

The *Belmont Report*,[16] regarded by U.S. federal agencies as the basic statement of principles for ethical research, established the principles of respect for persons, beneficence, and justice as the quintessential requirements for the ethical conduct of research involving human subjects. *Belmont* grounds informed consent in the moral principle of respect for persons, which requires researchers to honor the free, autonomous choices of prospective subjects and provide additional protections for vulnerable subjects.[14]

Respect for persons and their autonomous choices, as described in the *Nuremberg Code* and the *Belmont Report*, emphasize the right of self-determination in U.S. law, which holds that prospective subjects have a right to make free and autonomous "yes" or "no" choices with respect to their becoming involved in medical research.[10]

COMPONENTS OF INFORMED CONSENT

The *Belmont Report* points out that the moral foundations of informed consent logically include the following three elements: (1) *disclosure* of relevant information on the part of researchers and (2) *comprehension* and (3) *voluntariness* on the part of prospective research participants.[16] The disclosure of information occurs through discussions and dialogue with prospective research participants about material information concerning the study. Questions are asked and answered through these discussions and dialogues, as well as through consent forms and accompanying informational materials. Comprehension is facilitated through careful attention to the process of communication between research participants and investigators, as well as other knowledgeable persons. Voluntariness is ensured if the research subject's agreement to participate is secured under conditions that are free from coercion and undue influence.

Disclosure

The purpose of disclosure is to provide sufficient information that will allow individuals to decide whether they wish to participate in the research. This information must include descriptions of the pertinent procedures used in the research, as well as descriptions of the reasonably foreseeable risks or discomforts and benefits of these procedures and information about appropriate alternative treatments (45 CFR 46.116; 21 CFR 50.25).

Comprehension

A prospective research participant's comprehension of information about the trial can be enhanced by presenting the material in a manner that is adapted to his or her mental capacities, level of education, language skills, emotional needs, cultural background, and social situation. Comprehension by the prospective participant also depends on the communication skills of those who are securing informed consent, and it is optimized when information is described in organized and thoughtfully planned presentations and repeated conversations.

Comprehension is also affected by a prospective participant's state of health, level of pain and discomfort, and emotional state. The informed consent *process* ideally provides ample time and opportunities for the prospective research participant to ask questions about the details of the trial and about his or her physical, emotional, social, and ethical concerns in relation to the trial.[14,15,19]

The informed consent *form* achieves the primary goal of protecting the dignity and autonomy of research participants when it effectively discloses material information about the research study in a manner that facilitates comprehension by the participants.[14] IRBs should review the content, format, and coverage of the informed consent form to ensure that the information is complete, accurate, and presented at an appropriate reading comprehension level. The informed consent form should not be constructed primarily as a legal document that serves to protect the institution and the researcher from liability. Hence, informed consent forms should not be overly long, complex, or jargon-filled.

Voluntariness

The third dimension of informed consent—the voluntariness, or free power of choice, of prospective research participants—requires that consent be obtained under conditions that are free from coercion, undue influence, and unjustified pressures. The *Belmont Report* defines and briefly discusses external factors that undermine consent, such as excessive rewards or inducements, overt threats, and undue pressure from members of the research team or from close relatives. Beyond external influences, internal issues can and often do influence a prospective research participant's decision to participate in research. Levels of pain, personal suffering, and desperation in the face of overwhelming illness can greatly influence the choices of prospective research participants.[20]

When risks are high, when uncertainty exists, when procedures are complex, and when patients who are prospective research participants are desperate, researchers may find it necessary to

expend extra effort to ensure that prospective research participants do, in fact, comprehend the disclosed information and have made a voluntary choice to enroll in the research.[14,21,22] The best way to ensure comprehension and voluntariness is to develop and follow an effective consent process.

THE INFORMED CONSENT PROCESS

The task of fully disclosing information regarding xenotransplantation is especially challenging, given the complexity and experimental nature of xenotransplantation, the risks to both xenotransplantation recipients and their intimate contacts (see box under "Intimate Contacts"), and the extraordinary demands placed on subjects whose physical and emotional health may already be compromised. Moreover, consent for this or any procedure is inadequate if the prospective subject does not truly understand the information provided or if coercion or misleading information is used. Although these concerns are not unique to clinical research involving xenotransplantation, the complicated nature of xenotransplantation research and the possible attendant public health risks require careful consideration of the informed consent process. Included in this consideration should be the content, setting, format, and pacing of the communication that occurs. It may also be advisable to include in these discussions certain individuals in addition to the subject, such as his or her family members and intimate contacts. Inclusion of these individuals must be voluntary and in accord with the subject's confidentiality and privacy rights.

The entire informed consent process should be aimed at providing a prospective subject with adequate information concerning the study, as well as with the opportunity to consider all of his or her options; answering the prospective subject's questions; ensuring that he or she comprehends the information that has been provided; obtaining the prospective subject's voluntary agreement to participate; and continuing to provide information as the participant or the situation requires. To be effective, this process should provide ample opportunity for the investigator and the subject to exchange information and ask questions. The final signature on an informed consent form is not an end in itself, but rather displays the essential information that was provided to the participant.

The following recommendations apply to interactions involving prospective adult research participants who are mentally competent to provide informed consent and who are considering enrollment in a xenotransplantation protocol in non-urgent situations. In the event that prospective subjects need to be considered for xenotransplantation on an urgent basis, modifications to the informed consent process may be necessary.

Points to Convey in the Informed Consent Process

In addition to elements of informed consent that are specifically required by applicable federal regulations and local requirements, discussions to facilitate obtaining an individual's informed consent to undergo xenotransplantation should include the following:

- Background and history of the particular procedure, including previous related trials and outcomes and relevant results from animal studies

- A description of the procedure(s) to be followed, including identification of those that are experimental

- A description of the risks and potential benefits, if any, of the procedure

- Available alternatives (both accepted medical practices and other experimental approaches), including their comparative risks and benefits

- Possible social, economic, psychological, and/or medical consequences to the subject and his or her family

- Measures to protect, and the potential for breaches of, the privacy and confidentiality of research subjects

- Responsibilities of the recipients of xenotransplantation products, such as the need for lifelong follow-up; collection, testing, and archiving of biological samples; behavioral modifications; the continued need to inform intimate contacts; and deferral of donation of blood and other body fluids and tissues

The Informed Consent Team

Due to the medical complexity of xenotransplantation, the lifetime commitment expected of the recipient, and the potential public health, psychosocial, and financial issues associated with the procedure, the informed consent process should involve a team of individuals with the expertise to educate the potential recipient about each of these areas. The individual members of this "consent team" may need to arrange separate meetings with the prospective subject to minimize the risk of overwhelming him or her with too much information at one time. The consent team should facilitate the subject's comprehension of the information that has been provided by encouraging discussion and raising open-ended questions about the xenotransplantation procedure.

Furthermore, the consent team should use the discussions with the prospective participant to determine whether the individual is entering into the study voluntarily, rather than in response to pressure from family or other external sources. Approaching the informed consent process as a two-way exchange is more likely to achieve the vital goal of protecting a prospective participant's rights and well-being.

At a minimum, the consent team should include the principal investigator, who provides basic medical and scientific information about the xenotransplantation procedure; an individual who is knowledgeable about post-transplant care and the long-term responsibilities of xenotransplantation recipients; and an individual(s) with expertise in the social, psychological,

and financial implications of xenotransplantation. The potential recipient should be informed that others may also be consulted to help address additional issues related to xenotransplantation, such as a religious advisor, a recipient of a xenotransplantation product, and a physician who is independent of the research team.

Factors That Facilitate the Informed Consent Process: Setting, Format, and Pacing

In order for members of the consent team to convey, and prospective participants to comprehend, the volume of complex information involved with xenotransplantation, special attention may need to be paid to the setting in which informed consent occurs. When the research is complex and/or includes factors such as high risk and seriously ill patients, a series of discussions are necessary. Discussions should:

- Take place in a setting that affords privacy, comfort, and freedom from disruption;
- Be face-to face, not excessively lengthy, and separated in time to allow the prospective subject to assimilate the information provided at each meeting; and
- Use language, both written and oral, at the level of the prospective subject's understanding, with medical and scientific jargon kept to a minimum and translated in the language with which the prospective subject is fluent.

Given individual differences in learning, efforts should be made to use more than one form of educational media, such as videos, diagrams, and pamphlets. Prospective research participants should be given ample time at each meeting to raise questions and share concerns about the xenotransplantation protocol.

To provide support to prospective subjects and to facilitate their retention and comprehension of information, they should be encouraged to include their significant others or other advisors in discussions about xenotransplantation. The inclusion of subjects' significant others also provides an opportunity for family and other intimate contacts to learn about the impact that xenotransplantation may have on them. With the prospective subject's consent, separate discussions between the consent team and the prospective subject's significant others provide the latter with the opportunity to ask questions and address concerns (e.g., their potential risk of contracting infectious diseases from the participant).

INFORMED CONSENT FORMS

The signing of consent forms is often overvalued in that often it is virtually equated with informed consent.[14] The signing of a consent form is neither the goal nor the end point of the informed consent process, but rather a single element in a larger, multifaceted strategy of disclosure, comprehension, and voluntariness.[11] Placed in this perspective, consent forms can and should play important roles in the overall consent process. The role of the consent form

includes confirming disclosure of essential information to prospective research participants and assisting them to comprehend this information.

Consent forms must contain the basic information required by 45 CFR 46.116 and 21 CFR 50.25. Guidance documents on xenotransplantation[1,23] from the U.S. Public Health Service (PHS), the DHHS, and the Food and Drug Administration (FDA) may assist investigators in developing additional information for inclusion in an informed consent document for these research studies. These particular guidances address the need for subjects to inform their future intimate contacts of those contacts' potential risks of infections originating from source animals, the need for subjects to indefinitely defer the donation of blood and other body parts, and other issues that are dealt with in the informed consent outline provided in this document.[23]

Informed consent forms should convey information in ways that will help ensure understanding. Consequently, they should be written in short, plainly worded sentences that employ familiar words and active verbs (see box) and use a format that is characterized by easily read print and print size, lowercase letters, and simple, frequent headings and subheadings.[1,11,12,14,24–27] They should use ordinary language, explain technical terminology, and be formatted in ways that facilitate comprehension and recall. Deficiencies in consent forms can contribute to failures to ensure truly informed consent.[14]

Sample Wording in Consent Forms

Wording about randomization: *"If you agree to be in this study, you will be in one of two groups by chance."* Or, *"You have a fifty-fifty (50%) chance of being in one of the two groups just described."*

Wording regarding alternative treatments: *"If you decide not to be in this study, you will receive the regular methods of care that we have talked about with you and that you have been receiving."*

In what follows, the SACX proposes a model for a clear, well-formatted, comprehensive, and understandable consent form for xenotransplantation protocols. The topics in **bold print** in the following form represent suggested headings (**CAPITALIZED**) and subheadings (**Lowercase except for first letter**). The actual headings and specific content of a given consent form will vary from this format according to the particulars of a given xenotransplantation protocol. (For example, all of the consent elements in the following form may not be applicable to an individual who will receive human skin cells grown on mouse feeder layer cells, or to his or her intimate contacts.)

The text that follows is formatted with narrower margins and in slightly larger print, is subdivided frequently, and uses titles and terminology that are familiar to most English-speaking persons. In general, sentences that are easily understood should be about 15 words long on average. The following outline reflects the influence of an article on consent forms by Hochhauser,[27] who showed that many words that are familiar to investigators and IRB members—such as *clinical*, *orally*, *placebo*, *protocol*, and *regimen*—are in fact rarely used and unfamiliar to many patients and prospective research subjects. Hochhauser[27] and other helpful sources[28] also recommend replacing terms often used by medical professionals, such as *abstain*,

discontinue, *new indication*, *uncommonly*, and *specimens*, with more familiar terms, such as *avoid*, *stop*, *new use*, *rarely*, and *samples*. In the outline that follows, some of the more technical words that are frequently used in consent forms and that are often, but wrongly, regarded as commonplace are placed in brackets after more ordinary words.

ADULT INFORMED CONSENT FORM:
PROTOCOL NUMBER _____: [OFFICIAL TITLE]

The informed consent form's introductory sentences and paragraphs should give both the official title of the research study [protocol] and a lay interpretation of that title, followed by the names of the institutions, agencies, and companies that are responsible for what the participants are being asked to do [the study sponsors].

The introductory section should also provide the following information:

1. A clear statement that this is a medical research study [clinical research] and what the study is about.

2. An overview of what is to follow. In this paragraph, prospective participants are told that they will be informed about:

- The purposes of the study and how it will be done [the study's procedures or steps];
- Standard or regular treatment choices [alternative treatments] that are available to patients who do not enroll in the research study;
- Risks and potential consequences for those who enter the study [study participants] and their family members and partners,
- The known and potential benefits; and
- The rights and responsibilities of those who choose to enroll in the project.

3. A statement regarding the process of consent, such as: "The doctor leading the research team and other people involved in this research study will be discussing these topics with you. We want you to ask questions about anything you do not understand. We want to make sure that you understand and agree with everything in this consent form before you sign it."

PURPOSES

This brief section should provide the following information:

1. A specific and clear description of the purpose(s) of the study.

2. A general description of the prospective subject's medical problem or condition [diagnosis] that would make it possible for the prospective subject to be considered as a candidate for enrolling in/signing up for the study. Details about the criteria for being included or excluded from this study are given below under the heading "Participation."

TREATMENT CHOICES (ALTERNATIVES TO ENROLLMENT)

This section should contain a description of the regular treatment and/or disease-moderating [palliative care] choices that are available to those who decide not to enroll. This topic, which is usually placed near the end of consent forms, should be moved forward in order for prospective subjects to consider their options early in the consent process and to be able to compare them with the research that is being proposed. Suggested wording is as follows:

> Even if you decide that you do not want to be in this study, you will continue to receive care for your illness or condition. This care will include standard treatments (for example, ...). [The list of examples will depend on the condition being treated.]

PARTICIPATION

The first brief paragraph under this heading should specify the number of persons/participants to be enrolled at the potential subject's site and, if pertinent, the total number of enrolled persons, if this is a multi-center study. Also included should be the survival rates of subjects who have undergone the same xenotransplantation procedure and the rates of complications that have occurred in these subjects. It is suggested that this section also contain the following subheadings:

1. **Who can enroll (inclusion criteria)**
   This section should describe the physical [physiologic] standards or criteria that make a participant eligible for enrollment. It also should explain that the study will enroll only those who indicate that they are committed to comply with a follow-up [post-procedure] plan that includes a variety of hospital visits and tests. This plan may include multiple blood draws, muscle biopsies, and other samples and tests. [Details about the follow-up procedures that are required are

found below under the subheading "Surveillance," under the headings "Study Procedures" and "Responsibilities."]

This commitment is necessary because the potential risks of xenotransplantation experiments require researchers who are doing the study to keep track of [monitor] the health of those who are enrolled. The informed consent form should clearly state that acceptance into this research project depends on the prospective participant's prior agreement and good-faith commitment to comply with these obligations.

2. Who cannot enroll [exclusion criteria]

Exclusion criteria should include the following information:

a. A description of medical problems, conditions, or characteristics that cause persons not to meet the standards discussed immediately above

b. A statement that those who are unwilling or unable to comply with the required follow-up [post-procedure] plan [regimen] just discussed and spelled out below will not be included in the study

c. A statement that the criteria that will keep persons from being enrolled are unrelated to a person's gender, race, religion, or national origin

3. Duration of involvement

Involvement in this study has two phases: (a) the amount of time taken by the medical procedures and treatments described under the heading "Study Procedures" below; and (b) the lifelong participation expected of everyone who receives a xenotransplantation product. Everyone who enrolls has the right to withdraw at any time from the medical procedures and treatments included in (a), but once they receive a xenotransplantation product, lifelong monitoring and involvement, such as regular medical checkups, appropriate notification or education of new intimate contacts and new health care providers, etc., are expected. Details of this lifelong involvement are given below under the heading beginning with the words "Voluntary Enrollment."

4. Chance assignment [randomization] to treatment groups

If all persons who are enrolled in the research project will not receive the experimental treatment, it should be explained that each subject will be

assigned by chance [randomized] into one of the various treatment groups (see wording below), each of which should be described. For example, if those who enroll are equally divided into two treatment groups, one of which will not receive the experimental treatment, then all enrollees should be informed that there is, for example, a 50% chance that they will not receive the experimental therapy. Suggested wording is as follows:

> If you agree to be in this study, you will be assigned to one of two groups. Your placement in either of these groups will be determined by chance. [Or, "You have a fifty-fifty chance of being placed in either group."]

STUDY PROCEDURES

The term *study procedures* refers to the series of steps that will be followed in this research study. The following subheadings represent common procedures that should be listed and addressed under this heading:

1. **Screening visits, assessments, and tests**
   These procedures include those that will be used by the medical team to evaluate who can be enrolled [suitability of enrollment]. Possible discomforts associated with evaluations and tests should be mentioned. The subject should be informed whether test results will be made available to him or her.

2. **Rating scales**
   If rating scales will be used in determining who can be enrolled in the study and/or the medical progress of subjects during the study, this section should describe the general nature of the rating scale and process.

3. **Surgical or medical procedures**
   A description of the procedures that will be used in the xenotransplantation procedure should be outlined in wording that laypersons can understand. Possible [potential] discomforts and side effects should be addressed.

4. **Medications**
   The purposes of all drugs [pharmacologic agents] required by the research project should be described. Some of these drugs may deal with immunosuppression, which has to do with moderating and keeping the body from attacking the xenotransplantation product. Similar to the "Surgical procedures" subsection above, this information should be presented as clearly

and briefly as possible; there could also be a cross-reference to the discussion of the risks associated with these drugs ("Risk section," subsection "Immunosuppression and other drugs used in the study").

5. Diaries

Prospective participants should be informed if they will be asked to keep a record of or track their temperature, vital signs, weight, and/or any symptoms they experience. This subsection should also disclose who will read these physical diaries and how long they will be kept.

6. Follow-up

The prospective participant should be informed that the PHS recommends that persons who receive xenotransplantation products are expected to accept a number of lifelong responsibilities (see "Responsibilities"). These include regular physical checkups, during which samples of their blood and other tissues are taken. This subsection should describe the schedule and method for collecting these specimens, how the specimens will be collected (particularly any procedure that is more than minimally invasive), in what manner and who will be responsible for the cost of this follow-up, and what measures are or will be in place to protect the privacy of subjects and to maintain the confidentiality of information.

RISKS

In addition to describing the risks associated with invasive procedures such as surgery, this section should provide a comprehensive evaluation/assessment of the risks associated with the project or protocol itself. This section is a crucially important part of the informed consent document.

1. Rejection/failure of the procedure

First, an estimation of the chance that the proposed xenotransplantation procedure will not work, and the consequences of that failure—including the possibility of death—should be forthrightly disclosed. Second, the results of previous trials with this or a similar xenotransplantation product should also be disclosed, including relevant [pertinent] information about serious sickness [morbidity] and death [mortality] in previous studies. Third, how rejection of the xenotransplantation product or the appearance of rejection will be dealt with medically [managed] should be addressed. Fourth, this subsection should

address other [alternative medical] options (if any) that will be utilized in the event that the experimental therapy fails, or if it turns out that the subject did not receive the xenotransplantation product due to chance assignment [randomization].

2. Immunosuppression and other drugs used in the study

This subsection should explain what immunosuppression is and the drugs that either will be used or are likely to be used in the study. An outline of these drugs and their risks should be provided under this heading. Investigators should consider giving details about infrequent risks and side effects associated with these drugs in an appendix.

3. Animal-to-human (xenogeneic) infections

This subsection should explain that animal-to-human [xenogeneic] infections are one of the potential risks to study participants and the participant's close contacts. The following wording might be used:

> Although precautions against your developing this type of disease have been and are being taken, there is still a chance that you could become infected. The level of that risk is not known at present. Beyond your personal health, there is the possibility that you could transmit an infectious disease to family members, health care professionals, and the public.

Subjects receiving a pig (porcine) xenotransplantation product should be told specifically that studies have indicated that some pig viruses can be transmitted from pig cells to human cells in a test tube [in vitro]. Because the results are inconclusive, the participants should be informed that there is insufficient information on the basis of prior xenotransplantation trials to assess the risks of xenogeneic infections. To reduce these risks, volunteers for this study, as well as intimate contacts, are expected to follow safety precautions, such as long-term or lifelong medical checkups; refraining from donating blood, sperm, or other body fluids, (for example, breast milk); restricting behavior with intimate partners to reduce the risk of transmission of infectious disease to partners and, possibly, to fetuses; and other precautions outlined in detail below under the heading "Responsibilities."

4. Possible discomforts and quality-of-life issues

The discussion of these topics will vary from one study to another. Researchers should acknowledge that limited information is available concerning the effects

of a xenotransplantation procedure on the participant's quality of life, and they should neither understate nor overstate potential discomforts or quality of life consequences.

5. Possibility of being isolated or quarantined

This subsection should explain that, if a xenotransplantation recipient acquires an infectious disease that poses a serious and immediate threat to others, public health laws could necessitate isolation or quarantine.

6. Loss of confidentiality

This subsection should explain that loss of confidentiality is a risk because of several of the duties of those who volunteer to be enrolled in the study—in particular, lifelong monitoring and the storage of blood and tissue samples—and the possibility that a serious event, such as an infectious disease outbreak, could necessitate examination of study participants' medical information. FDA is authorized to examine study records and the underlying medial records, even if there is not "serious event." The informed consent document should specifically mention this, for example, "There should be a statement that notes the possibility that the Food and Drug Administration may inspect the records." Possible results of disclosure of participant's confidential information (for example, adverse impact on employment, insurance) should also be discussed, as should the possibility of legal recourse in the event of unauthorized disclosure.

7. Possibility that this study will be ended early

This section should explain the possibility that the study could be ended before the whole study plan is completed. For example, the company and/or university that is in charge of [sponsoring] the study could stop the study for financial reasons or because the research question is answered more quickly than expected (or because of immediate adverse effects). The likely effects of an early ending to the study should be explained to the subjects. For example, an early end of the study could mean that the participant, rather than the sponsor, would be responsible for the health care costs arising from this research project.

8. Additional risks

A final statement should say that, beyond the risks that are disclosed above, it is possible that this study involves additional risks to the subject that are currently unknown and unforeseeable.

RESPONSIBILITIES

This section should explain that participants in this research would be expected to accept a number of future responsibilities if they choose to enroll. These include the following important items:

1. Regular checkups

2. The necessity of informing researchers of changes in address and telephone numbers

3. Timely reporting of all unexplained illnesses

4. Practices that limit the exchange of body fluids with intimate personal contacts and reduce the risk of transmission of infectious disease to fetuses

5. No future donations of blood, sperm, or other body fluids or tissues

6. Autopsy at death and informing family members and significant others of his/her agreement to autopsy

7. Education of family members and intimate contacts (with aid of the research team, if desired) about the following:
   a. Infectious disease risks
   b. Willingness to give blood samples and other specimens
   c. Agreement to follow precautionary measures, including agreement to refrain from donating blood or other body tissues and agreement to report any unexplained illnesses

8. Disclosure to future health care providers about the individual's receipt of a xenotransplantation product

9. Arrangements for assistance in meeting future responsibilities in the event that the subject loses decision-making capacity

This section should include assurances that a counselor and/or other member(s) of the research team will be available to assist those who volunteer to enroll with the education responsibilities.

This section should conclude with a reminder that xenotransplantation is a procedure with potential risks that extend beyond the recipient. Therefore, prospective subjects who display an unwillingness to comply with the required safety and monitoring measures [regimen] will not be allowed to enroll in this research project [will be denied entry into the protocol].

RIGHTS

This section should describe the rights of the individual in regard to the following:

1. Access to personal medical information
2. Updates on newly identified risks of the xenotransplantation product and/or procedure
3. If the study included a placebo control, whether or not, after a determined period, subjects in the placebo arm will be informed of their status and relieved of the responsibilities of lifelong surveillance, tests, and follow-up
4. Recourse under the law for loss of confidentiality

POTENTIAL BENEFITS

This section should list reasonably foreseeable benefits, including the likelihood of benefits, or that there are no foreseeable benefits.

COSTS AND COMPENSATION

This section should describe both costs and compensation to the subject that will result from participation in the study.

CONFIDENTIALITY

This section should describe the measures that are planned to protect the confidentiality of medical information. These measures must be in accordance with applicable laws, including the privacy rule promulgated under the Health Insurance Portability and Accountability Act (HIPAA). It should inform the

recipient of the long-term need for access to medical records by the appropriate health agencies (e.g., FDA, Centers for Disease Control and Prevention).[1]

VOLUNTARY ENROLLMENT ACCOMPANIED BY AN AGREEMENT TO FOLLOW (ADHERE TO) RESPONSIBILITIES

Suggested language for this section is as follows:

> "Your enrollment in this research is completely voluntary—that is, enrolling is something you choose to do, apart from any pressure from anyone else. Refusal to participate will involve no penalty or loss of benefits to which you are entitled, and you may stop [discontinue] participation at any time without penalty or loss of benefits to which you are entitled.
>
> "Unlike many other kinds of medical research, however, your voluntary decision to enroll in this study should be based on the recognition that, once you receive a xenotransplantation product, you are expected to fulfill future responsibilities that are part of [accompany] this research, as outlined above. Your dropping out [withdrawing] from this study may result in the discontinuation of financial support for lifetime checkups and other responsibilities, and could affect the function of any xenotransplantation product that may have been received (for example, if immunosuppressive drugs are discontinued)."

CONTACT INFORMATION

This section should provide the names and telephone numbers of persons to contact for (1) questions about the study and enrolling, (2) continuing information about medical questions and problems (complications) after enrollment, including reporting of unexplained illnesses that may be related to the research, and (3) information about research subjects' rights.

* * * * *

SPECIAL ISSUES RAISED BY XENOTRANSPLANTATION

Beyond the issues discussed above, researchers and IRB members need to know about special problems and concerns raised by xenotransplantation clinical research so that they can provide appropriate explanations in the consent forms and throughout the informed consent process.

Public Safety Measures

Lifelong Surveillance, Isolation, and Quarantine

Because xenotransplantation research presents the unquantified risk of spreading new infectious diseases, both conventional and innovative public safety monitoring measures may be needed. For example, if there is an imminent risk of casual transmission of infectious disease, it may become necessary to place the recipient of a xenotransplantation product in temporary isolation or long-term quarantine. The recipient is likely to require lifetime monitoring, including routine physical evaluations, laboratory testing, the archiving and future testing of tissue and/or body fluid specimens, and autopsy—even if the xenotransplantation product is rejected or removed. As a result, research participants need to understand and accept not only the complex inherent risks of the procedure, but also the extent to which necessary public safety measures may intrude upon their lives and those of their family and intimate contacts.

Public safety measures necessary for xenotransplantation research, such as lifelong monitoring and/or temporary isolation, seemingly conflict with current federal regulations that allow research participants to withdraw their consent for participation in the research at any time.[11] In the case of infection that poses an imminent public health threat, state laws can be invoked to achieve a recipient's compliance. Accordingly, to ensure that public health authorities are able to detect and isolate new infectious agents, it is essential for prospective xenotransplantation research participants to be fully informed that their compliance with lifelong surveillance is critical and that failure to comply may cause authorities to impose measures prescribed in public health laws, if warranted.

Public Health Laws

If it is determined that the recipient of a xenotransplantation product has an infectious disease that poses a serious and imminent health threat to others, and the recipient fails to voluntarily comply with public health protection measures, public health laws could be invoked to apply varying degrees of restraint on personal behavior, including detention and quarantine. The U.S. Supreme Court has clearly endorsed the authority of a state to enact quarantine and other public health laws.[29]

Under most state public health laws, physicians are required to report to public health officials both specifically identified and unidentified infectious diseases that may endanger the public's health. For example, New York statutes provide that "[a]ny disease outbreak or unusual disease shall…be reported to the State Department of Health."[30] An unusual disease is defined as "a newly apparent or emerging disease or syndrome of uncertain etiology that a health care

provider…has reason to believe could possibly be caused by a transmissible infectious agent or microbial toxin."[30] Once such a communicable disease is reported, most state laws give health departments broad discretion to take whatever steps are necessary to prevent and control its spread, including tracing the contacts of infected individuals and imposing isolation. Legal compulsion is rarely needed in this type of situation, however, because individuals tend to comply voluntarily with testing and control measures after they have been exposed to a potentially dangerous infectious agent

Accordingly, a physician providing care to a xenotransplantation recipient would be required to report an unidentified disease if there were reason to believe that it could be caused by a transmissible infectious agent and might pose a threat to public health. Thereafter, the health department could exert its legal authority to impose protective measures to prevent the spread of communicable disease. Since treating physicians and other health care professionals providing care to xenotransplantation recipients would serve as the first line of defense against a new disease emerging in a xenotransplantation recipient who failed to comply with surveillance requirements, it is important that public health authorities and health care professionals maintain good communication.

It is less clear that current public health laws effectively address situations in which a xenotransplantation recipient who manifests no symptoms of disease fails to comply with surveillance instructions. Under current public health laws, it would probably not be possible to conduct mandatory periodic monitoring of such individuals and their intimate contacts before the presence of a communicable disease becomes evident. In other words, if a recipient resists ongoing evaluation, he or she probably could not be legally compelled to comply, unless and until he or she demonstrates symptoms of a disease that poses a threat to public health. A comprehensive review of state public health laws with respect to xenotransplantation is currently under way (need current status, citation if completed). Recommendations for modifications of those laws are forthcoming.

Issues Involving Third Parties

The risks of transmission of infectious disease warrant serious consideration by all who may be put at risk—research participants, their intimate contacts, and health care workers (both those involved in the xenotransplantation procedure and those who later come in contact with the recipient or biological samples from the recipient). Informing research participants of these risks and obtaining their voluntary prior consent has become a legal and ethical standard in most parts of the world. Because xenotransplantation could pose a risk to people other than the research participant, however, some commentators argue that obtaining informed consent from research participants alone is not enough and that there is an ethical obligation to involve other individuals who could be at risk.[5] Currently, there is no legal foundation in the United States for obtaining informed consent from third parties, unless the study expressly includes third parties in the research.

Intimate Contacts

There are a number of obstacles to obtaining consent from intimate contacts of xenotransplantation research participants. For example, the research participant's intimate contacts may change over time such that, at some time after the xenotransplantation procedure, the recipient no longer has a close relationship with some individuals but has developed close relationships with a number of persons who were not intimate contacts when the procedure was performed. Tracking these changes over time could prove to be difficult or impossible. In addition, obtaining "consent" from intimate contacts of a xenotransplantation recipient would involve disclosure of confidential information about the recipient, which can occur only with the recipient's permission.

> **Intimate contacts** of the recipients of xenotransplantation products include persons who have engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with the recipient. Examples of intimate contacts include, but are not limited to, sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with percutaneous, mucosal, or other direct exposure. Sharing of housing or casual contact, such as hugging or kissing without exchange of saliva, would not be interpreted as intimate contact.[31]

In light of these difficulties, the informed consent process for xenotransplantation research should include a component that informs the recipient of his or her responsibility to educate current and future intimate contacts about the possibility of xenogeneic infections. Current federal guidance[1] recommends that, during the consent process, the consent team offer assistance in this educational effort and address uncertainties about the risks of xenogeneic infections, behaviors known to transmit infectious agents, and methods to minimize the risk of transmission (such as the use of barriers to transmission of infectious agents during sexual activity and the use of appropriate precautions for nonsexual contacts). Recipients should also be informed of the need to educate their current and future intimate contacts about the importance of reporting significant unexplained illness to the institution where the xenotransplantation procedure was performed, to their primary care provider, or to a local public health department.

Health Care Professionals

Health care workers who come in contact with xenotransplantation recipients also face the risk of xenogeneic and zoonotic infections. Accordingly, the informed consent process for xenotransplantation research should include a component that advises recipients of their responsibility to inform their current and any future health care providers about their receipt of a xenotransplantation product.

In addition, as is true of the recipient's intimate contacts, health care providers involved in the xenotransplantation procedure should be specifically informed in advance about the xenotransplantation procedure, the known potential and theoretical risks of xenogeneic infections posed by the procedure, behaviors known to transmit infectious agents from human to human, methods to minimize the risk of transmission, and the need to report significant unexplained illness to the institution where the xenotransplantation was performed. In addition, the sponsor and/or the clinical center where the xenotransplantation procedure is performed should develop plans for monitoring health care personnel. These monitoring plans can be used to educate the health care provider(s) in advance of the procedure (recommendations exist for collecting

specimens (both pre- and post-exposure) and storing personnel records for these health care workers.[1]

The sponsor and/or institution where the xenotransplantation procedure is performed should have written plans for post-exposure evaluation and management and should take steps to ensure that the plans are well understood by the health care worker before he or she agrees to participate. (For example, plans could address situations in which health care workers experience an exposure, such as an accidental needle stick, that involves the risk of transmission of an infectious agent.) Policies, protocols and monitoring plans should be tailored to the specific types of xenotransplantation performed and to the nature and circumstances of the health care worker contact; recommendations for action should be reevaluated periodically as knowledge of risk and appropriate preventive measures improves. Finally, recommended infection control measures should be strictly followed to reduce the risk of transmission of xenogeneic infections and other blood-borne and nosocomial pathogens.[1]

The Community

The notion of community consent for xenotransplantation research has been the subject of considerable controversy, both nationally and internationally,[32] and poses many difficulties. For example, how should the "community" be defined in a highly mobile, closely interconnected world, where infectious agents can and do spread rapidly across continents, and how could the "community" provide consent?

In light of the difficulty inherent in the notion of "community consent," SACX suggests that it or some other appropriately constituted advisory committee should continue to serve as the mechanism for ensuring ongoing education and discourse in the lay community about public health concerns, as well as other social, medical, and ethical issues raised by xenotransplantation clinical research. The meetings of this advisory committee should be open to the public and the news media, and its members should be freely available for interviews. Other activities that the advisory committee should undertake in fulfilling this charge include the following:

- Be informed about clinical xenotransplantation protocols (including the enrollment of research participants, safety data, annual progress reports, and filings of adverse events) so that it can knowledgeably communicate with the community about pertinent social, public health, medical, and ethical issues (except where such information may be confidential).

- Develop closer collaborative relationships with pertinent entities in other nations so that it can acquire and share with the public broader perspectives about pertinent social, public health, medical, and ethical issues related to xenotransplantation.

- Develop and make available informational resources on scientific, medical, social, ethical, and public health issues raised by xenotransplantation.

- Provide a forum for public discussion of such issues, when appropriate.

- Make recommendations to the Secretary on policy and procedures, following public involvement, and subsequent consensus developed by the committee's multidisciplinary membership.

The information that the advisory committee provides to the public must be authoritative, easy to understand, balanced, and comprehensive in order to maintain the public's trust.

Participation of Children and Incapacitated Adults

An autonomous agent is defined as "an individual capable of deliberation about personal goals and of acting under the direction of such deliberation."[16] The elements of informed consent (information disclosure, comprehension, and voluntariness) are core safeguards of research participant autonomy. Each of these elements is called into question when the prospective research participant is an impaired adult or a child who is not capable of comprehending disclosed information and appreciating the risks and benefits of and alternatives to participation. Recognizing this situation, the *Belmont Report* states that "special provisions may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of research participants that one might consider as incompetent should be considered on its own terms."[16]

Determining Decision-Making Incapacity

The determination of decision-making capability is a complex undertaking. An individual may have temporary, permanent, or fluctuating alterations of decision-making capacity. Moreover, individuals frequently change their minds about treatment options according to their experiences as diseases progress. Illness itself can be associated with impaired thinking in otherwise competent patients.[32] Because a patient's capacity to make informed decisions can vary during the normal course of disease, investigators must be able to recognize the difference between decision-making incapacity and normal response to illness.[20]

Clinically relevant examples include patients with acute or fulminant hepatic failure and those with chronic liver failure. Many patients with fulminant hepatic failure, often as a result of viral exposure or a drug reaction, experience altered mental status or hepatic coma due to circulating toxins in the later stages of their disease process. Patients with chronic liver failure also are at risk for changes in mental status as their disease progresses. In both of these clinical scenarios, liver transplantation from a human donor is an effective treatment, and mental competency returns. However, in this era of profound organ shortage, a suitable donor may not be immediately available. Xenotransplantation has been successfully used as a bridge to transplantation with human organs in both of these clinical situations.[33,34] Because of temporary mental impairment, patients enrolled in these types of protocols were incapable of providing informed consent, and consent was obtained from their legally authorized representatives.

Federal and Other Guidance in Clinical Trials

[NOTE: this section is being reviewed for accuracy and will be revised as appropriate]

Federal laws governing informed consent in research address situations in which some research participants may not be capable of rendering informed consent.[11,12] In October 1996, the FDA and the Office of Human Research Protections (OHRP) jointly recognized that for some types of emergency research (such as in acute treatments for stroke, seizure, burn injuries, etc.) it may be nearly impossible to secure all of the required elements for obtaining informed consent from prospective subjects in life-threatening medical situations. FDA issued regulations (21 CFR 50.24) and OHRP issued guidance (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc97-01.htm) to permit an exception to the requirements for informed consent for certain types of emergency research. These regulations require the investigator to obtain legally effective informed consent from the research participant or the research participant's legally authorized representative before entry into a clinical trial unless all of the following conditions exist:

- The prospective research participant is in a life-threatening situation,

- Informed consent cannot be obtained because of an inability to communicate with the prospective participant,

- There is insufficient time to obtain consent from the prospective participant's legal representative, and

- No alternative is available that provides an equal or greater likelihood of saving the prospective participant's life.

Under these emergency circumstances, the investigator and another physician who is not involved in the study are required to certify the existence of all four conditions listed above. In the event that there is insufficient time to poll an independent physician, the investigator may proceed in the best interests of the prospective research participant, but must then obtain the written review and independent evaluation of an independent physician within five working days. Documentation of the investigator's and independent physician's certification must be submitted to the IRB. It is also the duty of the investigator to inform the research participant's legal representative that this individual's participation in the trial might be discontinued without penalty.

In addition, FDA regulations at 21 CFR 50.24a(7)i-v and OHRP guidance require that the investigator's protocol contain additional protections of the rights and welfare of the subjects, including:

- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn

- Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits

- Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results

- Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation

- If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator [will], if feasible, [attempt] to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Sections 312.30 or 812.35 of CFR Title 21.

FDA has issued a guidance document that may help to clarify the regulations regarding these issues, found at http://www.fda.gov/ora/compliance_ref/bimo/err_guide.htm. Investigators and IRBs should refer to the text of the emergency research regulations and guidance to ensure that they are compliant with the regulations.

With respect to the participation of incapacitated individuals in research in non-emergency situations, federal regulations do not specify criteria that a research participant's legally authorized representative should use in deciding whether to enroll the prospective participant in a clinical trial. The *Belmont Report*[16] does, however, outline the following criteria: the legally authorized representative should understand the incompetent subject's situation, act in the person's best interest, and have an opportunity "to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest." Although state laws accommodate medical decision making on behalf of an incapacitated or incompetent patient by a legal guardian, health care agent, or other surrogate decision maker, most of these laws do not address the question of when a legally authorized surrogate decision maker may enroll an incapacitated person in a research study. Neither state nor federal laws fully resolve the myriad ethical, social, and moral implications of including decisionally impaired individuals in research. There has been a significant amount of interest in addressing the gaps in managing this issue for vulnerable groups, particularly for persons with mental illness[35–37] and for children.[38–42]

Xenotransplantation for Incapacitated Adults

The process of obtaining informed consent in the context of xenotransplantation is further complicated when consent would need to be rendered by a legal surrogate or proxy decision-maker on behalf of an incapacitated research participant. Based on the criteria set forth in the *Belmont Report*,[16] the decision to enroll another individual in a xenotransplantation clinical trial must take into account both the short-term consequences for the transplant recipient, such as discomfort or frequent blood draws, as well as the long-term consequences, including the requirements for lifelong follow-up and autopsy and the risks and benefits of available alternatives. In addition, this decision must be made on the basis of the public safety issues that attend xenotransplantation research.

Considering all of these factors, the SACX recommends that at this time, enrollment of mentally impaired individuals into xenotransplantation protocols should be limited to those in whom mental capacity is likely to be restored by the procedure. In these circumstances, the incapacitated patient may participate in xenotransplantation research if the surrogate decision-maker has evidence that the individual would have wanted to participate in the xenotransplantation protocol, or if the surrogate decision-maker determines that the individual's enrollment would promote the patient's best interests. In addition, the surrogate would need to consider and possibly provide evidence that the patient is a responsible party in normal circumstances and is likely to adhere to lifelong follow-up requirements. The research team should be assured that there are plans for assistance in meeting these requirements, in the event that it is needed. Formerly incapacitated patients who regain capacity after a xenotransplantation procedure need appropriate information to ensure that they understand and accept their responsibilities with respect to public health precautions outlined in the consent form.

Participation of Children in Xenotransplantation Research

A child is defined as an individual "…who [has] not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."[11] Hence, the definition varies by state. For example, in North Carolina, the age of adulthood is 21 years.[43] In Alabama, the age of adulthood is 18 for married citizens and 19 for those who are unmarried.[44]

Informed consent for research has been the subject of considerable debate in the field of pediatrics.[45] The complexity of delineating appropriate decision-making roles for the child and his or her parents or guardian increases as the child develops.

At this time, given that clinical xenotransplantation research is in the earliest experimental stages, and given the commitment of lifelong medical monitoring required of all xenotransplantation research participants, the SACX recommends that, as a general matter, children should not participate in xenotransplantation protocols. However, there may be exceptions to this general rule, such as special circumstances in which the potential benefit to a child from a xenotransplantation procedure is high given the available alternatives. These situations should be considered on a case-by-case basis, and applicable regulations concerning children's participation in research must be followed. This recommendation is in accordance

with the requirement of 45 CFR 46.405 that parents or guardians can enroll their children into research that presents more than a minor increase over minimal risk only if that research holds the prospect of direct benefit for the individual subject. Enrollment of children under other circumstances would be allowed only after special review by the DHHS Secretary.[11] When children and adolescents who are otherwise eligible to enroll in a xenotransplantation protocol are sufficiently mature to comprehend the risks, benefits, and scope of commitment associated with xenotransplantation, their assent must be obtained, as required by federal regulation.[11]

RECOMMENDATIONS

1. The informed consent process used with respect to competent adults in clinical research involving xenotransplantation should ensure that (a) information disclosed is sufficiently complete, (b) the participant comprehends the information disclosed, and (c) the participant's consent to participate is voluntary.

2. The goals of the informed consent process should be facilitated by the following

a. Involving a "consent team" comprising (at a minimum) the principal investigator, a researcher team member who is knowledgeable about post-transplant care and the long-term responsibilities of recipients, and an individual(s) who has expertise in the social, psychological, and financial implications of xenotransplantation

b. Holding a series of face-to-face discussions with the prospective xenotransplantation recipient in a setting that affords privacy and comfort, and using comprehensible language

c. Using an informed consent form that includes specific elements required by the Common Rule as well as information recommended by the PHS, the DHHS, and the FDA and that is written in a manner that will help ensure understanding

3. To protect against the potential spread of new diseases, the informed consent process should include the prospective participant's understanding and agreement to comply with public safety measures (including lifelong monitoring, temporary isolation if indicated, and autopsy) and to inform family members, current and future intimate contacts, and health care personnel about the possibility of transmission of xenogeneic infection.

4. Public health authorities should maintain good communication with physicians and other health care providers who are likely to serve as the first line of defense against the spread of potential pathogens detected in xenotransplantation recipients.

5. Legislatures should evaluate the effectiveness of current public health laws to address situations in which an asymptomatic xenotransplantation recipient fails to comply with surveillance instructions, and they should consider appropriate amendments to those laws if needed.

6. Health care workers who will be involved in xenotransplantation procedures should be informed in advance of the known and potential risks of xenogeneic infections posed by the procedure, behaviors known to transmit infectious agents, methods to minimize that risk, the need to report significant unexplained illness, and the plans of the sponsor and/or the center where the procedure is performed for monitoring health care workers and for post-exposure evaluation and management.

7. The sponsor or institution where the xenotransplantation procedure is performed should produce and periodically update plans for monitoring involved health care workers and plans for post-exposure evaluation and management and should ensure that infection control measures are adhered to.

8. The SACX (or another appropriately constituted advisory committee) should continue to serve as a mechanism for ensuring ongoing education and discourse in the lay community about public health concerns, as well as other social, medical, and ethical issues raised by xenotransplantation clinical research, through the following:

a. Providing a forum for public discussion of xenotransplantation issues, as appropriate, and ensuring that the members of the advisory body are available for interviews;

b. Being informed about xenotransplantation protocols so that it can knowledgeably communicate with the community about pertinent social, public health, medical, and ethical issues;

c. Developing and making available informational resources on xenotransplantation;

d. Making recommendations to the DHHS Secretary on policy and procedures, following consensus developed by the committee's multidisciplinary membership; and

e. Developing closer relationships with relevant groups in other nations.

9. At present, enrollment of incapacitated adults into xenotransplantation protocols should be limited to situations in which:

a. The individual's mental capacity is likely to be restored by the procedure;

b. The individual's legally authorized surrogate decision maker determines that the individual's enrollment in the protocol accords with the individual's likely preferences under the circumstances or, if these preferences are unknown, that enrollment would promote the individual's best interests;

c. The individual's legally authorized surrogate represents that the individual is a responsible person and is likely to adhere to lifelong follow-up responsibilities; and

d. There are plans for assistance with life-long follow-up requirements in the event that such assistance is needed.

10. At this time, as a general matter, children should not participate in xenotransplantation protocols. There may be special circumstances, however, in which the possibility of benefit to a child is high, given available alternatives. Researchers and institutions should consider these situations on a case-by-case basis and should pursue further study of this issue.

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